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ORIGINAL ARTICLE

Pulmonary nodules at risk in patients undergoing liver transplantation for hepatocellular carcinoma

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Summary

The aim of this study was to evaluate the accuracy of pretransplant imaging in patients with hepatocellular carcinoma (HCC) considering small pulmonary nodules, and to determine whether preoperatively diagnosed small pulmonary nodules should be considered 'nodules at risk'. We evaluated 10 consecutive liver transplant patients with a diagnosis of HCC and pulmonary nodules detected by preoperative computerized tomography (CT) scanning. Pretransplant CT evaluation of pulmonary nodules showed a 90% accuracy rate. There was only one incorrect reading in the case of a patient, where a metastasis was misdiagnosed as a pulmonary fibroma. Two patients died from multifocal tumor recurrence with pulmonary metastases 17 and 19 months post-transplant. One more patient died 29 months post-transplantation on account of diffuse metastatic prostate carcinoma. Seven patients are currently alive with no evidence of tumor after a median follow-up period of 48 months post-transplantation. Small pulmonary nodules in high-risk HCC patients (low tumor grading, exceeding Milan criteria) may be characterized as *nodules at risk*, and evaluated very closely prior to listing and during the pre- and post-transplant periods.

Introduction

Liver transplantation (LT) is considered to be the treatment of choice for early hepatocellular carcinoma (HCC) in patients with end-stage liver disease. The acceptance of tumor-specific listing criteria [1] has led to 5-year survival rates among HCC patients comparable to those of patients transplanted for nonmalignant indications [2–4]. This has led to discussions about the potential expansion of these criteria, and the performance of LT for 'extended tumor indications' [5,6], especially in cases of live donors. As the presence of extrahepatic lesions constitutes an absolute contraindication for LT, there is a current emphasis on the detection of metastases by imaging studies [7–9].

The aim of this study was to evaluate the accuracy of pretransplant pulmonary imaging in HCC patients, and to determine whether any small preoperatively detected pulmonary nodules should be considered 'nodules at risk'.

Patients and methods

We analyzed data collected prospectively on patients transplanted at our Center with a diagnosis of HCC between April 2001 and July 2005. We specifically addressed pulmonary nodules detected by pretransplant imaging studies and categorized as granulomas. The term 'granuloma' was used to avoid the terms mass or lesion, which is automatically associated with malignancy.

Granulomas are benign lesions caused by infection or inflammation and can be seen as postinflammatory residua. In general, the criteria for benign lesions were: diffuse dense calcification, diagnostic criteria of hamartoma (round shape, smooth, regular contours, containing fat density, ±popcorn calcification) or benign-type calcification (i.e. central, target, laminated, concentric) [10]. All nodules included in this study showed either calcification, smooth contours or connection to vessels and size smaller than 10 mm.

All patients were examined using spiral-CT technology and intravenous contrast material. The delay for the start of the scan was 35 s in all chest examinations. Between February 2001 and August 2002, 4-detector-row spiral computerized tomography (CT) scanner (Siemens Somatom 4) with a collimator width of 2.5 mm was used. The scans were performed with a tube voltage of 120 kV and body weight adjusted tube current between 80 and 220 mA. The reconstruction interval in mediastinum and lung kernel was 5 mm each. Only in single cases, an older protocol with 8-mm reconstruction interval has been used. Since August 2002 a 16-detector-row spiral CT scanner (Siemens Somatom 16) was used, the scans were performed using a detector width of 1.25 mm. The scan parameter remained unchanged: the scans were performed with a tube voltage of 120 kV and body-weight-adjusted tube current between 80 and 220 mA. The reconstruction interval in mediastinum and lung kernel was 5 mm each. In cases with unclear findings, multiplanar reconstructions and thin-slice-reconstructions with 2-mm slice thickness were added.

Abdominal ultrasonography and bone scintigraphy were additionally performed in all patients. Serial alpha fetoprotein (AFP) levels were obtained prior to and after LT. Positron Emission Tomography (PET) scanning was not applied in these series, as all the patients showed multiple, smaller than 10-mm pulmonary nodules. This fact supports the assumption of benign pulmonary lesion, as it is known that the likelihood of a benign character is associated with the number of small pulmonary nodules [11].

Both deceased donor full-size LT (DDLT) and live donor LT (LDLT) recipients were considered. Evidence of extrahepatic tumor disease by pretransplant imaging constituted an absolute contraindication to LT.

All explanted livers were examined micro and macroscopically (0.5-cm thick slices) by an experienced pathologist. Tumors were classified according to the 6 Edition of the Tumor-Node-Metastasis System of the Union International Contre le Cancer (UICC) [12].

Follow-up studies included CT scans of the abdomen and chest, and measurement of AFP levels, every 4 months during the first year after transplantation, every 6 months during the second year, and yearly thereafter. Data collection was completed by July 31, 2007. Minimum follow-up was either 2 years or until death. No patient was lost to follow-up.

Results

Out of a total of 65 patients transplanted during the period of the study, data corresponding to 10 transplant patients with HCC and a diagnosis of small pulmonary nodules (all <10 mm) by pretransplant CT imaging studies were reviewed. Four additional patients (6%) without evidence of small pulmonary nodules in the pretransplant CT evaluation developed pulmonary metastases within the first two post-LT years. One of them, experiencing a prolonged and complicated course after LDLT, developed early pulmonary metastasis, within the first three post-LT months. The false negative rate of CT scan was 6%.

There were five men and five women with a median age of 57 years (range, 29–66 years). The etiology of cirrhosis was alcohol in two cases, hepatitis B in two instances, hepatitis C in three instances, and cryptogenic in the remaining two cases. One patient underwent 'salvage' living donor LT for HCC recurrence in a non-cirrhotic liver after a right trisectionectomy. Median Model for End-stage Liver Disease (MELD) score was 10 (range, 7–42). Four patients had solitary liver nodules with a median diameter of 3 cm (range 1.8–11 cm). Multifocal tumors with a median total diameter of 5.2 cm were detected in six patients. Seven out of the 10 patients fulfilled the Milan criteria (1 tumor ≤5 cm, 2–3 tumors all ≤3 cm, no vascular invasion) prior to LT by imaging studies.

Transarterial chemoembolization ($n = 1$) and radiofrequency ablation ($n = 2$) have been performed in three patients as 'bridging treatments' prior to LT. Both LDLT ($n = 6$) and DDLT ($n = 4$) were included in our series. Median AFP value was 33 U/ml (range, 4–1196 U/ml), with half of the patients having levels within normal laboratory range (<10 U/ml).

All the patients had uneventful postoperative courses. Two patients were UICC stage I, four patients stage II, and two patients stage IIIA. In two instances, no tumor staging was possible because of extended areas of tumor necrosis after bridging treatments. Vascular invasion was present in two patients. With the exclusion of the two cases with extensive tumor necrosis where no tumor grading was possible, HCCs showed well ($n = 2$), moderate ($n = 4$), and poor ($n = 2$) differentiation. Median follow-up period was 38 months (range 17–76 months). Two patients developed bifocal lung metastases 10 and 6 months post-transplant, respectively. They died from

Table 1. Patient characteristics.

Patient	Age (years)	Gender	AFP (U/ml)	LT	UICC stage	Grade	Milan criteria*	Immuno-suppression	Follow-up (months)	Metastases
1	59	M	9†	LDLT	NT‡	0	Exceeding	PT	76	No
2	55	F	114	LDLT	II	2	Meeting	PT	72	No
3	43	M	1196	DDLT	II	3	Exceeding	PC	19§	Yes
4	66	M	9†	DDLT	IIIA	2	Meeting	PC	29§	No
5	46	F	33	LDLT	II	1	Meeting	PT	51	No
6	53	F	6†	LDLT	II	1	Meeting	PT	48	No
7¶	62	M	77	LDLT	IIIA	3	Exceeding	PT	17§	Yes
8	63	M	57	DDLT	I	2	Meeting	PC	35	No
9	63	F	8†	DDLT	I	2	Meeting	PC	41	No
10	29	F	4†	LDLT	NT‡	0	Meeting	PT	24	No
P-value**	0.54	0.73	0.19	–	0.88	**0.0101**	**0.0157**	0.78		

LT, liver transplant; LDLT, live donor liver transplant; DDLT, deceased donor liver transplant; UICC, Union International Contre le Cancer Stage, 6 Edition; PT, Prednisone–Tacrolimus; PC, Prednisone–Cyclosporine.

*Radiological Milan criteria.

†Within normal laboratory range.

‡Total tumor necrosis after performance of bridging treatment.

§Patient died.

¶Patient with lung metastasis incorrectly interpreted as fibroma.

***P*-value according to the multivariate discriminant regression analysis. Significant values are presented in bold.

multifocal tumor recurrence 17 and 19 months postoperatively, i.e. 12 and 13 months after the diagnosis of the tumor recurrence in the lungs, respectively. One additional patient died 29 months post-transplantation on account of diffuse metastatic prostate carcinoma. The remaining seven patients are alive with no evidence of tumor after a median follow-up period of 48 months post-transplant (range, 24–75). Patient characteristics are outlined in Table 1.

All pre- and post-transplant CT imaging studies in patients with identified small pulmonary nodules prior to LT were independently evaluated by an experienced radiologist (HK). Median periods between the first diagnosis of pulmonary granulomas and LT, and the last CT scan and LT, were 62 days (range 18–334 days) and 35 days (range 0–67 days), respectively. A pulmonary metastasis, misdiagnosed as a small fibroma (opaque lesion with 3-mm diameter) prior to LT, was detected in one case (Fig. 1). This patient had bifocal pulmonary metastases diagnosed 10 months post-LT and died in the 17th post-transplant month. Re-study of the pre- and post-LT images corresponding to the other patient who developed lung metastases 6 months post-LT showed that the existing nodule remained stable and showed no association with the metastases (Fig. 2). The remaining eight patients were found to have stable findings (Fig. 3). The negative predictive value, i.e. the proportion of patients with negative test results who were correctly diagnosed, was 90%. Discriminant function analysis between seven variables (age, gender, AFP, UICC stage, grade, immuno-suppression and Milan criteria) was performed, giving a predictive value in the parameters tumor grade and Milan criteria (Table 1).

Discussion

The literature on LT has frequently addressed discrepancies between pretransplant tumor imaging studies and pathological findings based on the explanted liver [7–9,13], leading to disputes regarding the role of 'tumor number' and 'tumor size' criteria [5–7,13–18]. At the present time, given that both restrictive as well as inclusive groups agree that the presence of extrahepatic tumor constitutes an exclusionary determinant for transplantation [13–20], emphasis is being placed on the optimization of imaging techniques [7].

The recent availability of sophisticated radiological imaging during the pretransplant evaluation has led to a new clinical problem in the treatment of HCC patients: the diagnosis of small pulmonary nodules. In fact, the problem is more global, as the detection of nodules as small as 1–2 mm in diameter has become routine in the late 1990s. For example, the majority of smokers who undergo thin-section CT have been found to have small lung nodules, most of which are smaller than 7 mm in diameter [21]. The etiology of pulmonary nodules is diverse, comprising not only tumoral, infective and inflammatory disorders, but also vascular and congenital causes. The most common malignant lesions are pulmonary metastases and primary bronchopulmonary carci-

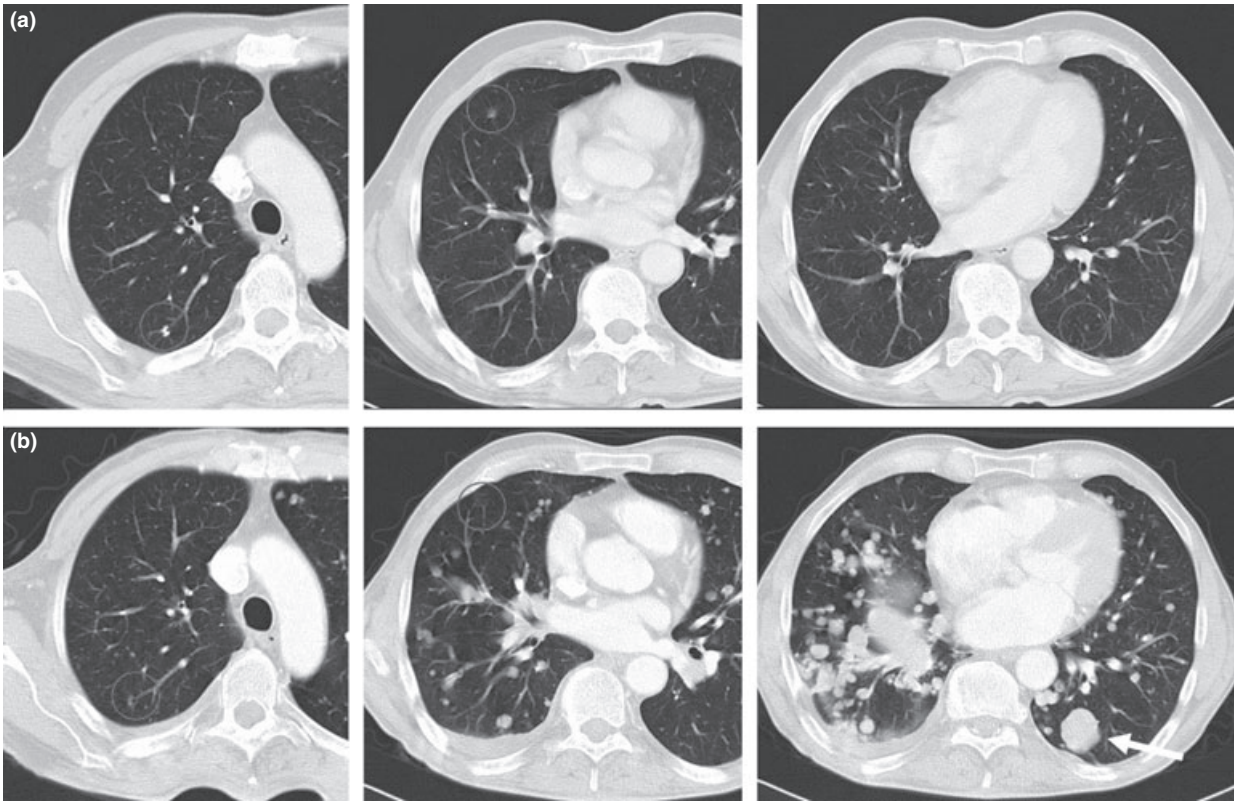

Figure 1 Patient no. 7 showed three small pulmonary nodules with different patterns on contrast-enhanced CT (a-lung window, high resolution kernel, 5-mm slice thickness). One lesion with calcification in right lower lobe, one lesion with 'nonsolid' density in the right upper lobe and one opaque lesion with 3-mm diameter in the left lower lobe. The control 10 months after LT (b–lung window, high resolution kernel, 5-mm slice thickness) showed multiple new intrapulmonary metastases in both lungs with unchanged appearance of the both previously diagnosed lesions in the right lung. The very small lesion in the left lung showed massive enlargement and was diagnosed as metastasis.

noma. However, the majority of small nodules are benign, of which 80% are granulomas or intrapulmonary lymph nodes [22]. The doubling time of most malignant solid nodules is between 30 and 400 days. Nodules displaying more rapid or slower doubling times are typically benign in origin. Radiological stability, either on chest radiography or CT, over a period greater than 2 years implies a doubling time of at least 730 days, which is generally considered to be a reliable indicator of a benign lesion [10]. Although there are already some guidelines for the management of small indeterminate pulmonary nodules, according to their prior probability of malignancy [10], in patients with a suspected or known cancer, the nodule could be secondary to a pulmonary metastasis and must therefore be managed according to a protocol adapted to the clinical situation. In such a situation, repeated surveillance CT examinations may be indicated to study the growth of the nodule [10].

As images, on many occasions, cannot clearly differentiate between benign lesions and very small HCC metastasis, follow-up studies are usually recommended in the clinical practice, but are not helpful in making a decision whether 'to transplant or not to transplant'. Besides, short waiting periods for patients with HCC and cirrhosis [23] render such 'wait and see' policies impractical.

A point of criticism to these series may be the fact that no PET scanning was performed. In general, fluorodeoxyglucose (FDG)-PET has shown very good results in defining the nature of singulary pulmonary masses with an accuracy of approximately 90% [24]. Nevertheless, the use of FDG-PET in the diagnosis of HCC lesions remains questionable, as HCC lesions show a very variable FDG uptake ranging from reduced uptake compared to the surrounding liver tissue to clearly pathologic FDG-enhancement in the lesion. In the last decade several groups have examined the use of FDG-PET for HCC detection with different results. There are clear statements that the sensitivity for HCC detection is low [25]. Other groups found the sensitivity of PET in diagnosis of HCC to be 55% compared to 90% for CT scanning, although only PET detected some types of tumors, including

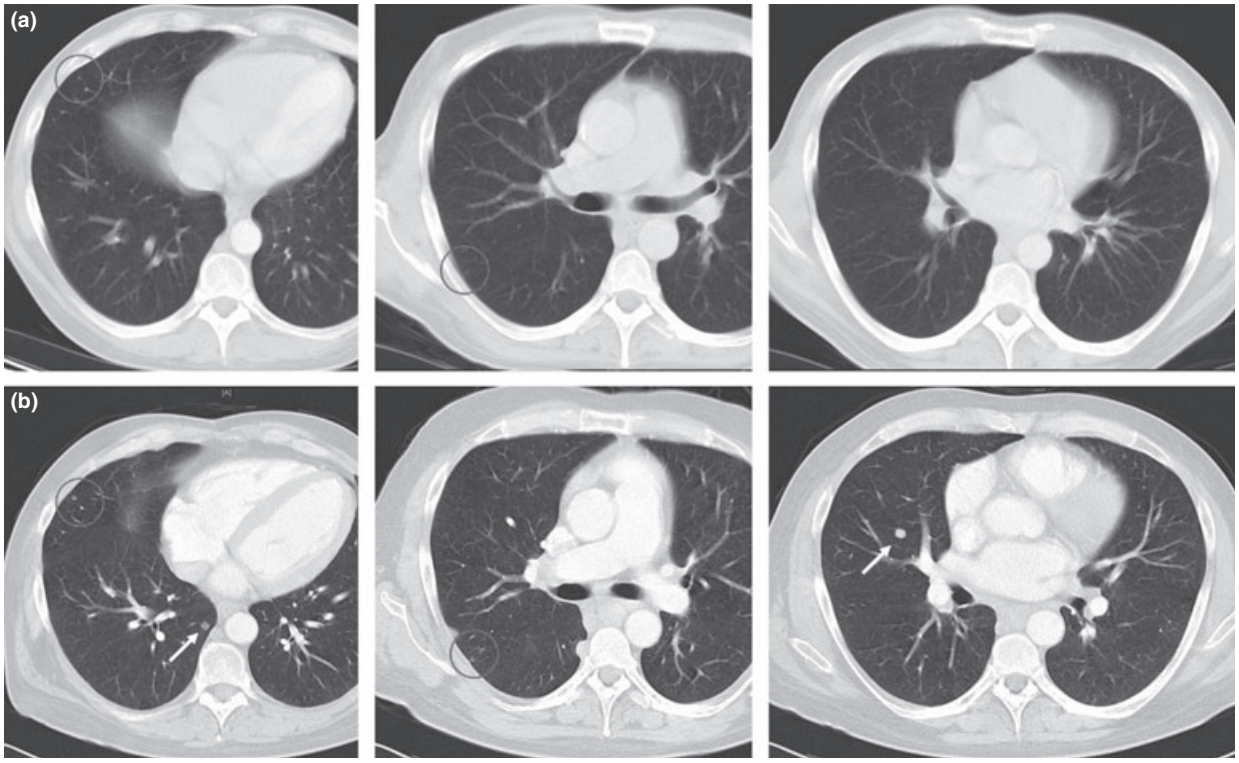

Figure 2 Patient no. 3 showed in the contrast-enhanced CT 42 days prior to DDLT (a–lung window, high resolution kernel, 8-mm slice thickness) two very small lesions in the right middle and lower lobe, each with 2-mm diameter and nonsolid density. The control CT 6 months post-LT (b-lung window, high resolution kernel, 5-mm slice thickness) showed multiple new intrapulmonary metastases in both lungs, but the initially found two lesions unchanged.

distant metastases [26]. Well-differentiated and low tumor grades had lower activity on PET and correspondingly lower PET scores. The same holds true for using FDG-PET for the detection of extrahepatic or pulmonary metastases of HCC. The detection rate of FDG-PET was found to be 83% for extrahepatic metastases larger than 1 cm in greatest diameter and only 13% for lesions less than or equal to 1 cm [27,28]. This discrepancy can easily be explained with the technical base of PET scans. The currently available detectors have a spatial resolution of minimum 5 mm. In addition, the PET scan per bed position (i.e. width of detector ring, currently 15 cm) needs 1–4 min, depending on scanner generation. On account of this much time taken, the patients will be examined with constant shallow breathing, which leads to movement of small lesions and further reduction of the spatial resolution. In our institution, there is experience in using FDG-PET since the late 1990s and in combined imaging with PET/CT since 2001. As all of our patients had multiple lung nodules smaller than 1 cm, we did not include a PET or PET/CT scan to further evaluate these patients.

To the best of our knowledge, our study is the first to address this clinical problem, describing the accuracy of the radiologic diagnosis and providing information on the long term outcome of HCC patients transplanted with such pulmonary nodules. We have included only patients with a minimum post-transplant follow-up of 2 years, which is considered to be a reliable indicator of a benign lesion. Although stable imaging results were detected in nine out of 10 patients in a median follow-up period of 38 months, based on the findings of the discriminant regression analysis, we believe that small pulmonary lesions presumed to be granulomas should be characterized as 'nodules at risk' if they are present in addition to poorly differentiated HCC or to HCC exceeding the Milan criteria. Certainly, because of the small volume of the study, these results should be validated from other study groups. However, it seems that a 'wait and see' policy in high-risk patients, i.e. patients with small pulmonary nodules combined with poor tumor differentiation or with HCC outside the Milan criteria, has to be applied. In these instances, a control CT within 3 months of diagnosis of small pulmonary nodules may be of cardinal importance, before the patient can be listed for LT. During this time, changes of the characteristics of the small pulmonary nodules or progress of the HCC in the

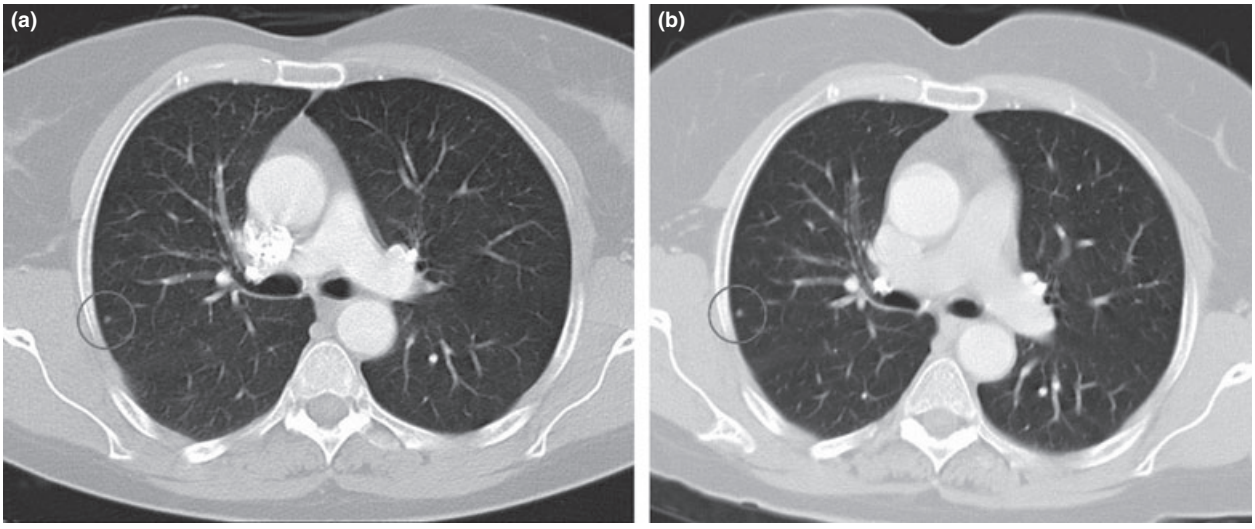

Figure 3 Patient no. 6 showed in the chest CT 24 days prior to LDLT(a-lung window, high resolution kernel, 5-mm slice thickness) a small pulmonary nodule with round shape and 3-mm diameter. This lesion remained unchanged in the control CT 4 years after LT (b-lung window, high resolution kernel, 5-mm slice thickness).

liver may forewarn to abandon the transplant possibility. Detection and close observation of these nodules prior to listing and during the pre- and post-transplant period is mandatory. Further reports from other centers may lead to the development of a corresponding transplant policy.

Authorship

GCS: wrote the paper. HK: analyzed radiological data. GS: analyzed data/statistical analysis. EPM: contributed important reagents/paper drafting. SB: performed the follow up. VRC: collected data. HAB: performed research/study. KJS: performed the histological analysis. CEB: designed study. HL: designed and performed research/study.

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